REMARKS

Claims 1-35 appear in this application for the Examiner's review and consideration.

Rejection under 35 U.S.C. § 103 (a)

Claims 1-35 were rejected under 35 U.S.C. § 103 (a) as allegedly obvious over U.S. Patent No. 5,149,538 to Granger *et al.* ("Granger"). Applicants respectfully traverse this rejection.

Granger discloses a misuse-resistive transdermal opioid dosage form, and states "[t]he present invention overcomes the deficiencies of the prior art dosage forms by providing a transdermal dosage form containing an opioid and an opioid antagonist, wherein the opioid and the antagonist are physically separated by an impermeable barrier. This barrier prevents undesirable ion exchange and other interactions between the opioid and the antagonist." (Granger, col. 1, ll. 59-66). Granger is silent with regard to the use of a combination of antagonists wherein both an adverse agent in the form of a free base and an adverse agent in the form of a pharmaceutically acceptable salt of the adverse agent are present.

In contrast to Granger, the present invention discloses and claims a transdermal dosage form which comprises an active agent or a pharmaceutically acceptable salt of an active agent in combination with both an adverse agent in the form of a free base and an adverse agent in the form of a pharmaceutically acceptable salt of the adverse agent.

Further, unlike Granger, the present invention does not require that the antagonist materials are separated from the active agent by means of an impermeable barrier. In fact, the present invention discloses that the active agent and the antagonist free base and antagonist salt may be dispersed throughout the reservoir of the transdermal device (*See*, *e.g.*, Page 10, ll. 2-5). Granger relies on its impermeable barrier to preclude delivery of the antagonist under normal usage, and discloses "[t]he impermeable barrier separates the opioid in the dosage form from the antagonist substance to prevent any adverse chemical reactions or ion exchanges between the opioid and the antagonist, and to prevent release of the antagonist unless the dosage form is ingested or immersed in water, alcohol or other solvent." (Granger, col. 2, ll. 54-59). In contrast to Granger, the present invention discloses that "[t]he Antagonists, which may be present anywhere in the polymer matrix, on the other hand, either do not diffuse out of the polymer matrix, or, if diffusion takes place, in an amount insufficient

to inhibit the analgesic effect of the active agent." (Page 10, ll. 21-24). Instead, the delivery rate of the antagonist combination of the present invention is partially controlled by the rate of diffusion of the antagonists out of the polymer matrix. (Page 10, ll. 18-20).

A finding of obviousness under 35 U.S.C. §103 requires a determination of: (1) the scope and content of the prior art, (2) the level of ordinary skill in the art , (3) the difference between the claimed subject matter and the prior art, and (4) whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1, 17 (1966). Therefore, obviousness inquiries require determining whether the prior art suggests the claimed invention and whether that prior art would have indicated a reasonable expectation of success to one of ordinary skill in the art. *In re O'Farrell*, 853 F.2d 894, 902-903, 7 USPQ2d 1673, 1680-1681 (Fed. Cir. 1988). Furthermore, "the prior art must teach or suggest all of the claim limitations." MPEP §§2142, 2143, emphasis added.

The Examiner has the burden of establishing a *prima facie* case of obviousness by proving three elements: (1) a particular reference (or combined references) must suggest or teach all the limitations of the challenged claim, (2) a suggestion or motivation from the prior art to modify or combine the reference teachings, and (3) a reasonable expectation of success must exist from the prior art. M.P.E.P. §§2142, 2143, citing *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Care must be exercised not to use the applicant's disclosure to fill in the gaps of the prior art. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

As the Examiner has agreed, Granger is silent with regard to the use of an active agent and a combination of adverse agents which comprises an adverse agent in the form of a free base and an adverse agent in the form of a pharmaceutically acceptable salt of the adverse agent. Further, no suggestion is found in Granger that the antagonist combination of the present invention could be used in a transdermal patch device without the use of an impermeable barrier which separates the active material from the antagonist materials. Thus, Applicants respectfully submit that Granger fails to teach or suggest all of the claim limitations, as discussed in detail above. Applicants respectfully submit that there is no suggestion or motivation from the prior art to modify the teachings of Granger to include, *inter alia*, the use of the combination of adverse agents which comprises an adverse agent in the form of a free base and an adverse agent in the form of a pharmaceutically acceptable salt of the adverse agent disclosed and claimed in the present invention.

Applicants respectfully submit that in view of the above remarks, the Examiner's rejection of claims 1-35 under 35 U.S.C. § 103 (a) over Granger has been overcome, and should be withdrawn.

Conclusion

In light of the above remarks, Applicants respectfully request that the Examiner reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney at (212) 692-1086, if a telephone call could help resolve any remaining items.

It is respectfully requested that the above remarks be entered into the file of the application. No fee beyond that for the extension of time is believed to be due for this amendment. The Commissioner is hereby authorized to charge any required fees to Duane Morris LLP Deposit Account No. 04-1679.

Respectfully submitted,

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